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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/848,852	Applicant(s) Hillman et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 4, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7, 9-16, and 46-49* is/are pending in the application.

4a) Of the above, claim(s) *1, 2, 11, 14-16, and 46-48* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *3-7, 9, 10, 12, 13, and 49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed April 4, 2003 (Paper No. 8) and the Declaration filed April 4, 2003 (Paper No. 9) in response to the Office Action of December 31, 2002 (Paper No. 7) are acknowledged and have been entered. Claims 3, 5, 7,9 and 12 have been amended. Claims 3-7, 9,10,12-13 and 49 are currently under prosecution.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following objections are maintained:

The Objection to the claims which recite limitations drawn to non-elected inventions.

Applicant argues that Applicant has a right by statute to claim his invention within the limitations he regards as necessary to circumscribe that invention with the proviso that the application comply with the requirements of 35 USC 112, and cites *In re Weber* wherein the Court has decided that 112, second paragraph allows the inventor to claim the invention as he contemplates it and therefor it is improper for the examiner to require removing the nonelected species of a Markush Group as a condition for examination of the elected claims and species. The argument has been considered but is not found persuasive to overcome the objection. The examined claims include limitations drawn to a non-elected invention. not drawn to a non-elected species . Further, the Examiner never required removing the non-elected invention as a condition for examination of the elected claims. The objection is maintained.

4 The following rejections are maintained:

Claim Rejections - 35 USC § 101

5. Claims 3-7, 9-10, 12-13 and 49 remain rejected under 35 USC 101 for the reasons previously set forth in Paper No. 7, Section 7, pages 5-8.

Applicant argues on page 8 that the instant invention has numerous practical, beneficial uses in toxicology testing, drug development and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. On page 9, Applicant argues that the Bedilion Declaration describes practical uses of the claimed invention in gene and protein expression monitoring applications which were well known at the time the patent application was filed and further those applications are useful in developing drugs and monitoring their activity. In particular the Bedilion Declaration states that the claimed invention is a useful tool when employed in a cDNA microarray. Further, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of knowledge as to the precise function of the protein encoded since the use of the claimed polynucleotide in gene expression monitoring applications is independent of its precise function. Further, at page 8, Applicants state that Dr. Bedilion, in the Bedilion Declaration, states that "the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray". This argument has been fully considered but is not deemed persuasive. First, the Examiner notes that the term "highly specific' in this context indicates that the hybridization would be highly specific, that is, that the sequence could be used to detect an exactly identical sequence. However, that is not the same as "specific' in the context of establishing utility: **any** sequence, regardless of origin or function,

can be used in such a 'highly specific' manner to detect a matching sequence; however, this is the very definition of a **non-specific** utility. A non-specific utility is a utility that can be attributed to any and all members of a class of compounds. In this case, the use for "specific' hybridization or detection can be performed with any nucleic acid. The fact that a microarray may have utility does not confer utility on any and all nucleic acids that might be assayed using the microarray. It remains that Applicants have disclosed no features or characteristics of the claimed SEQ ID NO:4, or the putative polypeptide encoded thereby, that would inform the experimenter as to what the significance of detecting that particular sequence would be. Detection of SEQ ID NO:4 under specific conditions using a claimed microarray would merely be an invitation to experiment further to determine what that result means, e.g. what significance the result has. Such an invitation to further experiment does not meet the utility standard of 35 USC 101.

While it is true that the claimed nucleic acids may be used in microarrays and in gene expression monitoring systems, the pertinent question is whether or not such use meets the criteria of 35 USC 101 as elucidated in MPEP2107, namely that the utility be specific, substantial and credible. The Examiner maintains that in the absence of any known biological function, or association with any disease state or condition, that the use of the claimed nucleic acids in microarrays is not specific or substantial as one would not know of what the results was indicative; if the claimed sequences were present in a microarray, and it was shown that a nucleic acid hybridized to the claimed sequence, what information would that impart? In the absence of any knowledge of the significance of the result, the Examiner maintains

that the use of the claimed nucleic acids in microarrays is not specific, as it could apply equally to any given nucleic acid and is not substantial, because the person of ordinary skill in the art would not be apprised of the significance of the result. The examiner notes that even if this were to be considered to be sufficient to meet the utility requirement under 35 USC 101, the scope of the claims would not be commensurate with such use, as such use would apply only to the exact, naturally occurring sequence and not to nucleic acids which vary from such by codon degeneracy (have different sequence, but encode the same protein) nor to nucleic acids 90% identical to the specifically disclosed sequence. With regard to "gene expression monitoring systems", the use of the claimed sequences in such systems is neither specific nor substantial, as, as argued above, such use could be argued for any naturally occurring sequence, and is not specific, nor is it substantial as the result would not be informative. It can be argued that the use of the claimed polynucleotides in either microarrays or in gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself: if the results of such experiments demonstrated that the claimed sequences were or were not present under particular conditions, such would be an invitation to experiment to determine why, which would seem to fall under the aegis of further experimentation to determine the properties of that which is being claimed.

Applicant summarizes case law on the utility requirement on pages 10 and 11 and states that the utilities of expression profiling, toxicology testing, drug discovery and diagnosis or treatment of cell proliferative disorders are sufficient utilities under 35 USC 101 and 112, first paragraph since they are well established, and the

Bedilion Declaration explains, in detail, the specific beneficial, and practical uses for the invention. Here the essential disagreement appears to be the interpretation of what constitutes a specific, substantial, and well established utility, as will be explained more fully below.

At page 9, Applicant states that the Examiner "contends that the claimed polynucleotides cannot be useful without precise knowledge of their biological function". It is noted that this argument is relevant to claim 4 and claim 49 (a), but does not fully apply to the other claims, i.e. if it were persuasive, the other claims would not be enabled in a manner commensurate in scope with the claims as only a small minority of the claimed species could be so used because as previously noted, such use would apply only to the exact, naturally occurring sequence and not to nucleic acids which vary from such by codon degeneracy (have different sequence, but encode the same protein) nor to nucleic acids 90% identical to the specifically disclosed sequence, nor to fragments of the disclosed sequence or fragments of degenerate sequences that encode fragments of the same polypeptide, since, if the sequence used in the assays is not the exact, naturally occurring sequence, determination of functional significance would not be possible.

Note that contrary to Applicant's assertion at page 9, there is no requirement being made by the Examiner that the "biological function" of the claimed polynucleotides be known to establish utility. It is noted that "biological function' may mean many things, including the ability to encode protein. The Examiner interprets "biological function" in this context to mean the actual activity of the protein encoded by the claimed nucleic acid, or the actual activity of the nucleic acid

itself, if it does not encode protein. Biological function is one of the factors that might be disclosed in establishing utility, but it is not required. Note that determination of the significance of the presence of the claimed nucleic acid in relationship to diagnosis, treatment or prevention of a cell proliferative disorder or inflammation would not require any knowledge of biological function; the mere correlation of the presence of the nucleic acid, in a manner that would be found to be credible by a person of ordinary skill in the art, with the presence of a disease or condition would clearly meet the requirements of 35 USC 101. Thus, Applicant's statement that there is a requirement made that Applicants disclose the biological function of the nucleic acid is incorrect.

Applicants summarize the Court's position on the utility requirement at pages 10-11 of the Brief. Applicants review of the issue of utility, the case law that has been cited and the holding that is found in the case law is not disputed. The only point of disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

At pages 12-13 Applicants argue that Dr. Bedilion explains the reasons why a person skilled in the art would have understood that the disclosed claimed polynucleotide is useful for gene expression monitoring application as a highly specific probe and that Dr. Bedilion explains that when developing new drugs for treatment of cell proliferative disorders , a person skilled would conclude that a microarray that contained the claimed sequence would be a highly useful tool and would have wanted their cDNA microarray to have a SEQ ID NO:3-encoding polynucleotide probe. The arguments have been carefully considered but have not

been found persuasive because as set forth above, the Examiner noted that the term "highly specific' in this context indicates that the hybridization would be highly specific, that is, that the sequence could be used to detect an exactly identical sequence. However, that is not the same as "specific' in the context of establishing utility: *any* sequence, regardless of origin or function, can be used in such a 'highly specific' manner to detect a matching sequence; however, this is the very definition of a *non-specific* utility. A non-specific utility is a utility that can be attributed to any and all members of a class of compounds. In this case, the use for "specific' hybridization or detection can be performed with any nucleic acid. The fact that a microarray may have utility does not confer utility on any and all nucleic acids that might be assayed using the microarray. It remains that Applicants have disclosed no features or characteristics of the claimed SEQ ID NO:4, or the polypeptide encoded thereby, that would inform the experimenter as to what the significance of detecting that particular sequence would be. Detection of SEQ ID NO:4 under specific conditions using a microarray would merely be an invitation to experiment further to determine what that result means, e.g. what significance the result has. Such an invitation to further experiment does not meet the utility standard of 35 USC 101.

At page 14 Applicants state that "Given the fact that the claimed polynucleotides are known to be expressed, their utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight." and further argue that the utility of cDNA microarrays has been established. The argument has been fully considered but has not been found persuasive, Appellant's analogy to a scale is inaccurate. Using the analogy to a

scale, the Examiner would argue that it is the microarray that is analogous to a scale, as a scale may be used to measure the mass of any desired object, and a microarray may be used to detect the presence of any desired nucleic acid sequence. However, the fact that a scale is useful does not confer utility on any and all objects that might be weighted using that scale, and the fact that the microarray may have utility does not confer utility on any and all nucleic acids that might be measured using the microarray. It remains that Applicants have disclosed no features or characteristics of the claimed SEQ ID NO:4, or the polypeptide encoded therefrom, that would inform the experimenter as to what the significance of detecting that particular sequence would be. As stated above, detection of SEQ ID NO:2 under specific conditions using the claimed microarray would merely be an invitation to experiment further to determine what that result means, e.g. what significance the result has. Such an invitation to further experimentation does not meet the utility standard of 35 USC 101.

Beginning on page 15, Applicants cite several "Literature review published shortly after the filing of Hillman '725 application describing the state of the art", and that such "confirm, for example that the claimed invention is useful for differential expression analysis, regardless of how expression is regulated". The Examiner notes that these references, e.g. Rockett et al and Lashkari et al have not been previously cited, nor have they been made of record by Applicants in any information disclosure statement. The Rockett et al paper (Xenobiotica, 1999, 29(7):655-691), however, supports the Examiner's assertion that the use of the claimed nucleic acids in microarrays does not meet the requirement of being specific

and substantial. In the abstract of the paper, Rockett et al state "An important feature of the work of many molecule biologists is identifying which genes are switched on and off in a cell under different environmental conditions of subsequent to xenobiotic challenge. **Such information has many uses, including the deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures.**" (Emphasis added.). In essence, Rockett is teaching that the purpose of such 'open" microarrrays, wherein the function of the specific nucleic acids is unknown, as is the case for SEQ ID NO:4, is that the results of the experiment are to be used to decipher molecular pathways and facilitate the development of other experimental or diagnostic procedures. Such would seem to the Examiner to clearly fall under the category of use for further experimentation to determine the properties of that which is being claimed, in this case the further experimentation being to develop other procedures that would take advantage of the knowledge gained by the initial experiment, or to 'decipher' molecular pathways. Thus, it is clear from Rockett et al that, as asserted above by the Examiner, that the use of the claimed polynucleotides in either microarrays or in gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself; if the results of such experiments demonstrated that the claimed sequences were or were not present under particular conditions such would be an invitation to experiment to determine why, which would fall under the aegis of further experimentation to determine the properties of that which is being claimed. Similarly, the Lashkari et al publication does not support Applicants asserts: While Lashkari et al indeed teach that 'amplicons', or

portions of DNA amplified from the genome by PCR can be used by arraying onto glass for expression analysis, the entire context of the article has been ignored by Applicants: The very first paragraph of the paper states "This massive and increasing amount of sequence information allows the development of novel experimental approaches to identify gene function. The paragraph bridging the columns of that page states "Experimental analysis must be performed to thoroughly understand the biological function of a gene product." The same paragraph states "it is clear that novel strategies are necessary to efficiently pursue the next phase of genome projects-whole-genome experimental analysis **to explore gene expression, gene product function and other genome functions** (emphasis added)." Thus Lashkari et al are clearly teaching that sequences of unknown function or significance are used in such strategies **to learn more about the sequences themselves and the genes they represent**. The Examiner maintains that this is clearly further research of the type that is not sanctioned as fulfilling the requirements of 35 USC 101.

Applicants argue at pages 16-18 that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery and the diagnosis of disease and that these uses are "well established". Each of these uses will be addressed individually in that the facts and issues directed to each use are distinct and separable. First, Applicants argue that toxicology testing is a well-established utility, therefore, because the claimed polynucleotides could be used in this manner, the claimed invention possesses utility. The arguments have been considered but have not been found persuasive because although Applicants are not incorrect in the conclusion

that toxicology testing is a well-established use of polynucleotides, as clearly indicated on page 17 all nucleic acids and genes are "useful" in toxicology testing. Therefore, this is a utility which is nonspecific and would apply to virtually every member of a general class of materials, such as DNA. While this may be a well-established use of polynucleotides, it is not a well-established, specific, substantial and credible utility of the claimed invention. Use of the claimed polynucleotides in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent upon the pattern derived from the array and says nothing with regard to each individual member of the array. If the expression of Applicants' polynucleotide of SEQ ID NO:4, or the other claimed polynucleotides, is affected by a test compound in an array for drug screening, what useful information has been gained regarding a specific and substantial utility for SEQ ID NO:4 or the other claimed polynucleotides, as an individually claimed entity.

On page 17 Applicants point to an attached email from Dr. Cynthia Afshari to an Incyte employee indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects and all expressed genes have a utility for tocxicological screening. The argument has been considered but has not been found persuasive because this is a utility which is nonspecific and applies to virtually every member of the general class of DNA. While this may be a well-established use of polynucleotides, it is not a well-established, specific, substantial and credible utility of the claimed invention. Use of the claimed polynucleotides in an array for toxicology screening is only useful in the sense that the information that is gained

from the array is dependent upon the pattern derived from the array and says nothing with regard to each individual member of the array. If the expression of Applicants' polynucleotide of SEQ ID NO:4, or the other claimed polynucleotides, is affected by a test compound in an array for drug screening, what useful information has been gained regarding a specific and substantial utility for SEQ ID NO:4 or the other claimed polynucleotides, as an individually claimed entity.

Applicants argument of the use of databases containing nucleic acid sequence information at pages 17-18 is noted and has been fully considered but is not deemed persuasive, as it is the nucleic acids themselves which are being claimed and not a database which is an informational representation.

At page 19 Applicants reiterate arguments drawn to Applicant's contention that Examiner's primary rejection is based on the premise that the claimed polynucleotides cannot be useful without precise knowledge of their biological function. The arguments have been considered previously but have not been found persuasive for the reasons set forth above.

At page 19, Applicants argue that the claimed invention has identifiable benefit in view of the Bedilion Declaration. The argument has been considered but has not been found persuasive for the reasons set forth above, drawn to the Bedilion Declaration.

At page 20, Applicants argue despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the family of expressed proteins, the Examiner refuses to impute the utility of the members of the family of expressed polypeptides to PAWES-2, SEQ ID NO:3. The argument has been considered but

has not been found persuasive because although it is clear that the putative encoded protein, if produced *in vivo*, would be a member of the family of expressed proteins, the specification as filed does not indicate that the encoded PAWES-2 is a member of any particular family and no evidence is presented in the specification that the claimed polynucleotide encodes a polypeptide in any particular family of expressed proteins. Thus although the expressed protein would be part of the family of expressed proteins, this does not impart either a specific utility or a substantial utility to the polypeptide encoded by SEQ ID NO:4 because this is a characteristic that applies to all proteins and further, additional experimentation would be required in order to determine if the expressed protein belongs to any particular family and if so, what function the expressed protein has if that family has a variety of functions. In particular, as stated in Paper No. 7, Section 7, pages 6-7,

> The asserted utility of the claimed polynucleotide appears to be based on the assertion that the polynucleotide encodes a polypeptide wherein the region of PAWES-2 (SEQ ID NO. 3), N285-H300 is similar to a Type I EGF motif signature and contains two cysteine residues characteristic of this motif and that the encoded polypeptide has a unique sequence from about amino acid 50 to about amino acid 59..... it is noted that the only specific information about PAWES-2, other than the sequence is that it has a region similar to a Type I EGF motif signature and a unique region. There is no indication that the Type I EGF motif signature is the consensus sequence for any particular function. There is no indication of the amount of homology of N285-H300 to the putative motif signature. Further, the polypeptide encoded by the claimed polynucleotide has 332 amino acids. The putative similar signature (with undefined similarity other than the two cited cysteines that are

> characteristic of this motif) comprises 16 of those amino acids which is 5% of the encoded polypeptide. The specification does not state that the claimed polynucleotide encodes a Type I EGF protein or that the encoded polypeptide has any homology to a Type I EGF protein,

Although Applicant argues that Examiner does not contradict the evidence that the claimed polynucleotide encodes a polypeptide in the family of expressed polypeptides, it is not clear why Examiner would have been expected to contradict evidence that was not presented in the specification as originally filed. It appears that the only family to which the putative expressed polypeptide might belong to is the family of expressed polypeptides and for the reasons set forth above, this connective imparts neither specific nor substantial utility.

On pages 20-21, Applicant argues case law drawn to the demonstration of utility by membership in a class. in particular Applicant argues that Examiner addresses PAWES-2, SEQ ID NO:3 as if the general class in which it is included is not the family of expressed polypeptides, but rather all polynucleotides or all polypeptides and that the family of expressed polypeptides is sufficiently specific to rule out any reasonable possibility that PAWES-2, SEQ ID NO:2 would not be also useful like the other members of the family. The argument has been considered but has not been found persuasive because, as previously set forth, Applicants have disclosed no features or characteristics of the polypeptide encoded by the claimed SEQ ID NO:4, that would inform the one of what use to put the encoded polypeptide. Again, although the expressed protein would be expected to be a member of the family of expressed proteins, this does not impart either a specific

utility or a substantial utility to the polypeptide encoded by SEQ ID NO:4 because this is a characteristic that applies to all proteins and further, additional experimentation would be required in order to elaborate a functional use for the encoded protein.

At page 21, Applicant argues that the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool rather than a object of research. The data generated in gene expression monitoring using the claimed invention as a tool is not merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells and potential drug candidates and toxins. Further, the claimed invention has numerous additional uses as a research tool including diagnostic assays and chromosomal mapping. The argument has been considered but has not been found persuasive because, as discussed above, whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed polynucleotide is not disclosed as having a specific activity, or having any property (such as a differential pattern of expression in diseased tissue) that can be specifically useful. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the utilities asserted for the claimed polynucleotide meets the three-pronged test of being specific, substantial and credible.

Beginning at page 22, Applicants argues that the claims have been rejected based principally on citations to scientific literature identifying some of the

difficulties in predicting protein function but none of the citations suggests that functional homology cannot be inferred by a reasonable probability in this case. In particular Applicant argues that the teachings of Bowie are irrelevant because they are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins and that these experiments are not relevant to Applicants use of amino acid sequence homology to reasonably predict protein function. Further Bowie et al support Applicant's use of amino acid sequence homology reasonably to predict the utility of the encoded polypeptide. Bowie et al teach that evaluating sets of related sequences which are members of the same gene family, is an accepted method of identifying functionally important residues which have been conserved over the course of evolution. Further, Applicant argues that it is known that natural selection acts to conserve protein function and conversely mutations that reduce or abolish protein function are eliminated by natural selection. In addition, Applicants argue on pages 22-23 that Lazar et al and Burgess at al are not relevant because they are drawn to mutagenesis of particular amino acid residues with known importance to function and are not analogous to molecular evolution which is profoundly influenced by natural selection and are likely to represent substitutions that do not alter protein function. On page 23 Applicant argues that partial loss of function does occur rarely in nature, however, this is a rare exception in evolution, not the rule and those partial loss-of-functions that are persistent still retain the utility of the non-mutant polypeptide. Applicant further argues that the Court has found that uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or

protein is not evidence of anything at all and that the mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence. Finally, Applicant argues that the literature cited by the Examiner is not inconsistent with Applicant's proof of homology by a reasonable probability and that Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability.

The argument has been considered but has not been found persuasive because no particular function has been ascribed to the encoded protein, PAWES-2, SEQ ID NO:3. Further, as disclosed above, the only specific information about PAWES-2, other than the sequence is that it has a region similar to a Type I EGF motif signature and a unique region. However, the only two amino acid residues that are similar to Type I EGF motif signature have been identified and there is no indication of the amount of homology , other than the two identified amino acid residues, of N285-H300 to the putative motif signature. Further, the polypeptide encoded by the claimed polynucleotide has 332 amino acids and the 16 amino acids of the putative motif comprise only 5% of the encoded polypeptide and it is unknown what function, if any, of the two identified amino acids might be conserved for natural selection. Further, given the information in the specification, the function of the encoded protein cannot be predicted since, as taught by Bowie et al, the amino acid sequence determines the shape and function of a protein and it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Further, since no related sequences

which are members of the same family have been identified, Bowie et al cannot support Applicant's use of amino acid sequence homology to reasonably predict the utility of the encoded protein. Again, it is unknown what function, if any, of the two identified amino acids might be conserved for natural selection. The Lazar et al and Burgess et al references, although drawn to site directed mutagenesis studies, clearly demonstrate that even a single amino acid alteration can alter the function of a protein. Although the court has found that a finding of a single amino acid substitution may drastically alter the function of a gene or a protein cannot be used as a matter of law to preclude an assertion of equivalence, the instant invention which encodes a 332 amino acid with a 16 amino acid region similar to a Type I EGF motif signature is not drawn to a molecule with a single altered amino acid. Given the known unpredictability demonstrated by the Lazar et al and Burgess et al references with their mutation analysis exemplifications, it is clear that one could not predict the function of any protein based on a 16 amino acid region similar to a Type I EGF motif which has two amino acids identified with that motif. This is not a single amino acid substitution, but apparently a substitution of 330 amino acids. Finally for the reasons of record, Examiner does not accept the assertion of utility based on homology and has presented evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability.

On page 24, applicant argues that although Examiner argues that the specification does not disclose whether the claimed polynucleotide or the polypeptide encoded by the claimed polynucleotide is associated with any disease. This is irrelevant. The claimed polynucleotide can be used for toxicology testing

without any knowledge of a disease. The arguments have been considered but have not been found persuasive because, as disclosed above, use of the claimed polynucleotides in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent upon the pattern derived from the array and says nothing with regard to each individual member of the array. If the expression of Applicants' polynucleotide of SEQ ID NO:4, or the other claimed polynucleotides, is affected by a test compound in an array for drug screening, what useful information has been gained regarding a specific and substantial utility for SEQ ID NO:4 or the other claimed polynucleotides, as an individually claimed entity.

At pages 25-26, Applicant challenges the legality of the Patent Examination Utility Guidelines. Since a Primary Examiner has no authority to comment on the legality of the Guidelines, this issue will be reserved for ruling by the Board of Patent Appeals and Interferences.

Applicant's arguments have been considered but have not been found persuasive for the reasons set forth above and the rejection is maintained.

Claim Rejections - 35 USC § 112

6. Claims 3-7, 9-10, 12-13 and 49 remain rejected under 35 USC 112 for the reasons previously set forth in Paper No. 7, Section 9, page 9.

Applicant argues that to the extent that the rejection under 35 USC 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 USC 101, it fails for the same reasons.

The argument has been considered but has not been found persuasive for the reasons set forth above, Applicants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the *prima facie* case of lack of utility. Applicant's arguments have been considered but have not been found persuasive for the reasons set forth above and the rejection is maintained. It is noted that even if utility were to be found for the nucleic acid of SEQ ID NO:4, the rejection of Claims 3-4, 6-7, 9-10, 12-13 under 35 USC 112, first paragraph would be retained because the urged utilities would apply only to the naturally occurring sequence and therefore that enablement of the urged uses of SEQ ID NO:4 is not commensurate in scope with Claims 3-4, 6-7, 9-10, 12-13.

7. Claims 3-7, 9-10 remain rejected under 35 USC 112 for the reasons previously set forth in Paper No. 7, Section 10, pages 9-11.

On pages 27-28, Applicant reiterates Examiner's statements that (a) because SEQ ID NO:4 is simply a polynucleotide fragment, it is not possible to determine what the ATG start site of any protein might be and it cannot be determined if the sequence would be in-frame to encode any protein and (b) there is no teaching whether any protein product is actually produced *in vivo*. Applicant argues that these assertions ignore the specification which teaches the exact amino acid sequence of the polypeptide encoded y SEQ ID NO:4 and which delineates the precise ATG start site and translation frame for the translation of the SEQ ID NO:3 polypeptide, thus there is no need for one of skill in the art to determine what the ATG start site might me. Applicant further argues that the nucleotide sequence of SEQ ID NO:4 which encodes the polypeptide of SEQ ID NO:3 was determined

from sequences from human cDNA libraries, thus the polynucleotide sequence of SEQ ID NO:4 is an expressed sequence and mRNA levels are routinely used as an indicator of protein expression. Further, mRNA levels are usually a good indicator of protein levels in a cell. The argument has been considered but has not been found persuasive because it is unknown if the polynucleotide sequence of SEQ ID NO:4 is an expressed sequence. SEQ ID NO:4 is a consensus sequence product of six clones derived from overlapping and/or extended nucleic acid sequences. SEQ ID NO:4 is not a polynucleotide that has been isolated from a living cell, it is a DNA fragment produced with recombinant techniques. Although it is clear that SEQ ID NO:4 as claimed encodes a protein, it is unknown whether the sequence is found in nature or is expressed in nature, or whether if it is expressed in nature, whether it encodes the expressed polypeptide of SEQ ID NO:3 in nature. As previously disclosed, the teachings of Alberts et al, Shantz et al, McClean et al and Fu et al demonstrate the unpredictability of protein expression based on mRNA. In addition, although the issue remains the same, in response to Applicants arguments, in support of the previous rejection Lewin (Genes VI, 1997, Oxford University Press, Inc., NY, pages 847-848 submitted with the response by Applicant) specifically teaches that the production of RNA cannot inevitably be equated with production of protein. Again, only solely in response to Applicants arguments, this is further evidenced by the findings of Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) who teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Applicant further raises the new issue that mRNA levelas are usually a

good indicator of protein levels in the cell. It is noted that contrary to Applicant's argument, the nexus of mRNA level to protein level in a cell is unpredictable. Again, solely in response to Applicants arguments, evidence abounds that this is known in the art, for example, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Carrere et al (Gut, 1999, vol. 44, pp. 55-551) teach an absence of correlation between protein and mRNA levels for the Reg protein. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-ranslational level. These references serve to demonstrate

that levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Because of the unpredictability of the art, protein expression cannot be based solely on mRNA expression.

Applicant further argues on page 29 that Lewin, *Supra*, teaches that for most genes, transcription is a major control point; probably the most common level of regulation and that the overwhelming majority of regulatory events occur at the initiation of transcription. Applicant further argues that it would be imprudent to assume that protein levels did not correspond to mRNA A levels and that the levels of SEQ ID NO:3 were controlled predominantly in a post transcription manner, thereby dismissing the significance of mRNA levels. The argument has been carefully considered but has not been found persuasive because it is known in the art that correspondence of mRNA levels and protein levels is not predictable.

Applicant further argues that there is no statutory requirement that an invention actually be reduced to practice to be patentable, since the polypeptide of SE ID NO:3 has been explicitly disclosed in the specification it meets the enablement requirement. Although there is no statutory requirement that an invention actually be reduced to practice to be patentable, for the reasons of record,

the claimed invention does not meet the enablement requirement. Applicant's arguments have been considered but have not been found persuasive for the reasons set forth above and the rejection is maintained.

6. Claims 3-4, 6-7, 9-10 and 12-13 remain rejected under 35 USC 112 for the reasons previously set forth in Paper No. 7, Section 11, pages 11-15.

Applicant argues on page 30-32 that the making of the claimed invention is enabled. The argument is noted but has not been considered because the scope rejection of Claims 3-4, 6-7, 9-10 and 12-13 under 35 USC 112 first paragraph imposed on pages 11-15 of the Office Action is not drawn to how to make the claimed invention, but rather, how to use the claimed invention.

Applicant argues on page 33 that the specification describes variants, and that such variants are useful for the same reason as SEQ ID NO: 4. This argument has been fully considered but is not deemed persuasive because the claims as written are not limited to naturally occurring sequences. Assuming that SEQ ID NO:4 is a naturally occurring sequence, Applicant's arguments pertaining to the use of naturally occurring sequence in toxicology testing or expression profiling, for example are limited to the use of just that: *naturally occurring*. It is not recognized in the art to use non-naturally occurring sequences for any of the uses urged by Applicants.

Applicant further argues on pages 33-35 that Bowie et al, Burgess et al and Lazar et al do not support the enablement rejection and that the Court has found that the uncontroversial fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all

and that the mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence. Applicant further argues on page 34 that while some amino acid substitutions can dramatically affect biological activity of a protein, the recited polypeptide encoded by the claimed polynucleotides have naturally occurring amino acid sequences and natural selection acts to conserve protein function and one would expect to be able to use the altered polypeptides in the exact same manner as one would use the nonaltered polypeptides, even though the results would not be exactly the same as if the none altered polypeptides were used.

The argument has been considered but has not been found persuasive because as disclosed above, the claims are not limited to naturally occurring polynucleotides and no particular function has been ascribed to the encoded protein, PAWES-2, SEQ ID NO:3 or any variant thereof. Further, as disclosed above, the only specific information about PAWES-2, other than the sequence is that it has a region similar to a Type I EGF motif signature and a unique region. However, only two amino acid residues that are similar to Type I EGF motif signature have been identified and there is no indication of the amount of homology , other than the two identified amino acid residues, of N285-H300 to the putative motif signature. Further, the polypeptide encoded by the claimed polynucleotide has 332 amino acids and the 16 amino acids of the putative motif comprise only 5% of the encoded polypeptide and it is unknown what function, if any, of the two identified amino acids might be conserved for natural selection. Further, given the information in the specification, the function of the encoded protein cannot be predicted since, as taught by Bowie et

al, the amino acid sequence determines the shape and function of a protein and it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. It is unknown what function, if any, of the two identified amino acids might be conserved for natural selection. The Lazar et al and Burgess et al references, although drawn to site directed mutagenesis studies, clearly demonstrate that even a single amino acid alteration can alter the function of a protein. Although the court has found that a finding of a single amino acid substitution may drastically alter the function of a gene or a protein cannot be used as a matter of law to preclude an assertion of equivalence, the instant invention which encodes a 332 amino acid with a 16 amino acid region similar to a Type I EGF motif signature is not drawn to a molecule with a single altered amino acid. Given the known unpredictability demonstrated by the Lazar et al and Burgess et al references with their mutation analysis exemplifications, it is clear that one could not predict the function of any protein based on a 16 amino acid region similar to a Type I EGF motif which has two amino acids identified with that motif, much less the function of a variant thereof. This is not a single amino acid substitution, but includes substitutions ranging from 5% to 95%%. The effects on the function of the polynucleotide or on the encoded polypeptide cannot be predicted for the reasons of record. Applicant's arguments have been considered but have not been found persuasive for the reasons set forth above and the rejection is maintained.

6. Claims 3-4, 6-7, 9-10 and 12-13 remain rejected under 35 USC 112 for the reasons previously set forth in Paper No. 7, Section 12, pages 15-18.

Applicant argues on page 39-40 that Applicants had full possession of SEQ ID NO:4 and SEQ ID NO:3 at the time of filing. The argument has been noted but has not been but has not been considered because the rejection is not drawn to either SEQ ID NO:4 or SEQ ID NO:3.

Applicant, on page 40 states that the Office Action alleges that Applicants did not possess the claimed invention because polynucleotides comprising SEQ ID NO:4 include full length genes which are not adequately disclosed in the specification. Applicant argues that full length genes are not explicitly recited in the claims. Although the phrase comprising does not exclude additional, unrecited elements, the use of this phrase does not result in the inclusion of any arbitrary element in the scope of the claim if such elements are not specifically recited. There is simply no requirement for the specification to include a detailed description of elements which are not explicitly recited by the claims. The argument has been considered but has not been found persuasive because Applicant is mischaracterizing the rejection, the rejection is not drawn to SEQ ID NO:4, but rather to the claimed variants which, as broadly written, read on genomic DNA for the reasons of record. Since the claims are open and read on genomic DNA, inclusion of genomic elements in determining the scope of the claims is proper.

At page 41, Applicant argues that naturally occurring sequences are not limited only to those sequences which are allelic variants of SEQ ID NO:4 but include any sequence that occurs in nature, from any species and it is improper for the Office to impose its own narrow definition of what the invention is and then conduct the examination based on this incorrect definition. The argument has been

considered and as drawn to Examiner's limitation to allelic variants, the argument is persuasive. However, it is clear that the disclosures of the body of the rejection are relevant not only to allelic variants, but also to species variants and the issues remain the same. It is noted that Applicants have described only a single naturally occurring sequence, that of SEQ ID NO:4 which encodes the predicted protein of SEQ ID NO:3. Applicants have provided no information or description about how conserved the gene in question is, that is, how similar the homologues from other species would be expected to be, nor have they described a single species other than the single allele (instance) of the gene as obtained from a single human. There is no description about the function of the gene nor the protein encoded thereby, such as would allow one of skill in the art to predict what portions of the disclosed sequence would be expected to be conserved. Accordingly, the mere recitation of "naturally occurring" does not obviate the issue raised with respect to written description. Similarly, with respect to claims to nucleic acids encoding proteins with 90% identity, again, no such naturally occurring variants have been disclosed, nor has any function been described for the encoded protein, nor ways in which the encoded protein might be altered while retaining that function. With further respect to this issue, it is a nucleic acid that is being claimed; without having a written description of all naturally occurring sequences within the metes and bounds of the claims, one would not be capable of determining whether or not a given species was claimed.

At page 42, Applicants argue that variants are described, for example, at pages 15-16, 18 of the specification. This argument has been fully considered but is not deemed persuasive. As drawn to allelic variants, page 6 of the specification

merely defines what an allelic variant *is*. It does not describe even a single naturally occurring allelic variant. Similarly, at pages 15-16, the specification merely describes some of the things that *may* happen to cause allelic variation, i.e. to give rise to 'naturally occurring' species within the scope of the claims. However, it is not true that one could find in nature any and all possible changes within a given gene, and the specification has described not a single naturally occurring variant of SEQ ID NO: 4. Further, even *if* the specification had described some naturally occurring human allelic variants within the scope of the claims, such would not be commensurate in scope with the claims since not a single sequence has been disclosed that is obtained from another biological species. Further, a recitation that the polypeptide comprises at least 60 contiguous nucleotides of SEQ ID NO:4 or a naturally occurring polynucleotide comprising sequences at least 90% identity to SEQ ID NO:4, is insufficient to meet the written description requirement.

At page 42, Applicants argue that "one of ordinary skill in the art would recognized naturally occurring variants of SEQ ID NO: 3 having 90% identity to SEQ ID NO: 3"; this is not true. One could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO: 3, but that same person, handed a protein in a test tube, would have no way of determining whether that protein were 'naturally occurring'. The same applies to the nucleic acid of SEQ ID NO: 4.

At page 43-45 Applicants argue that the situation in this case distinguishes from that in *Fiers* and *Lilly* because the nucleic acids in those cases were defined based on functional characteristics, and not, as here, based upon chemical structure.

This argument has been fully considered but is not deemed persuasive because as a practical matter, the claims in both those cases were limited to the naturally occurring sequences encoding particular proteins, which proteins are well known by their functions. In this case, Applicants claims require no such conserved function. Given that, to take the claim from *Fiers* cited by Applicants, the person of ordinary skill in the art would immediately recognize that any and all species within the metes and bounds of "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide" would encode proteins with *greater* than the 90% identity claimed by Applicants; the person of ordinary skill in the art would not expect to find that great an amount of variation within a single species, while still meeting the functional limitation of being a human fibroblast interferon-beta polypeptide. Thus, the claims in both *Lilly* and *Fiers* were of *narrower* scope than the claims in question here. However, similar to the case here, both *Lilly* and *Fiers* involved disclosures of only a single sequence. Accordingly, the parallels to the instant case are clear. Thus, while recitation of structure is indeed an important factor, mere recitation of structure (90% identity to nucleic acid or the protein encoded thereby) and a product-by-process type of limitation ("naturally occurring"), without even a limitation to the biological species from which the single disclosed nucleic acid of SEQ ID NO: 4 was obtained or a recitation that the polypeptide comprises at least 60 contiguous nucleotides of SEQ ID NO:4 or a naturally occurring polynucleotide comprising sequences at least 90% identity to SEQ ID NO:4, is insufficient to meet the written description requirement.

At page 46, Applicants argue that the claims "do not define a genus which is "highly variant"". Applicants argue that the Brenner reference states that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues, and that the present invention is directed to polypeptides related to the amino acid sequence of SEQ ID NO:3 and polynucleotides related to the nucleotide sequence of SEQ ID NO:4 and that since the claims are drawn to polypeptides encoding naturally-occurring amino acid sequences having at least 90% identity to Seq ID NO:3, , this variation is far less than that of all potential PAWES-2 proteins related to SEQ ID NO:3, that is those PAWES-2 proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:3. The argument has been considered but has not been found persuasive because Brenner's calculations represent theoretical assessments and can form the basis of a hypothesis, however these calculations while providing evolutionary information do not establish the relationship of a protein biologically without a second criterion such as function, or location, or occurrence, or associated expression. Therefore, in the instant case, Brenner's calculations and applicants' analogy are well accepted as two distinct facts, but do not apply to the current grounds of rejection of lack of written description of the claimed genus described only by the chemical structure of one member without a description of how that structure correlates with the definitive properties of the genus encompassed.
To elucidate further, appellant is misdirecting the issue. The issue here is not whether or not sequences 90% identical to SEQ ID NO: 3 or 4 would be considered to be evolutionarily related to such, but whether or not the specification as originally

filed provides an adequate written description of the 'genus'. While 90% identity is certainly sufficient to establish that two proteins are structurally similar and/or evolutionarily related, it is not predictive of function. Evolutionary relatedness merely means that two entities (proteins, nucleic acid sequences, or even whole organisms) are evolutionary descendants of a common ancestor. In the process of diverging, said proteins, nucleic acids or organisms take on different structures and functions. To follow Applicants argument to the level of organisms, it would appear that Applicants would urge that the written description of a monkey constitutes an adequate written description of a human, as the two are well known to be over 90% identical. The fact that the claims are drawn to 90% identity which is a scope more stringent than the threshold for evolutionary relatedness set forth by Brenner et al. is not relevant. What *is* relevant is that the specification as originally filed does not define a common structure or function that defines the genus claimed, and the written description is not commensurate in scope with all possible naturally occurring sequences at least 90% identical which would be expected to encompass evolutionarily related, but structurally and functionally distinct, genes and proteins.

At page 47, applicant argues that the art has matured considerably since the *Lilly* and *Fiers* cases. While this is true, it is not of consequence as regards this rejection for lack of adequate written description of the claimed genus. The key issue here is that applicants have disclosed a single nucleic acid sequence, which is expected to encode a single protein. No function has been attributed to either. The claims encompass all naturally occurring nucleic acid sequences that are at least 90% identical to SEQ ID NO: 4, or all nucleic acid sequences that encode proteins

90% identical to SEQ ID NO: 3 as well as all sequences that comprise at least 60 contiguous nucleotides of SEQ ID NO:4 or a polynucleotide that is at least 90% identical to SEQ ID NO:4. No defining characteristics have been disclosed to identify the critical features of the genus, and no species homologues or allelic variants have been described or disclosed. Further, Applicants own arguments of evolutionary relatedness would suggest that Applicant would urge that the disclosure of a single naturally occurring sequence is sufficient written description to entitle Applicant to claim the breadth of yet-undiscovered evolutionarily related but structurally and functionally distinct nucleic acids. Applicant's arguments have been considered but have not been found persuasive for the reasons set forth above and the rejection is maintained.

Claim Rejections - 35 USC § 102

6. Claims 3,6,7,9 remain rejected under 35 USC 102(e) for the reasons previously set forth in Paper No. 7, Section 15, pages 19-20.

Applicant argues on page 48 that amendment of claim 3 to recite "said fragment is at least five amino acid residues in length", obviates the rejection. The argument has been considered but has not been found persuasive because review of the sequence comparison, us-09-848-852-3.rni result 2, of record, clearly shows that the reference teaches a polynucleotide that encodes five amino acids of SEQ ID NO:3. Applicant has not submitted evidence to prove that the claimed product is different from those taught by the prior art. Applicant's arguments have been considered but have not been found persuasive for the reasons set forth above and the rejection is maintained.

10. All other objections and rejections recited in Paper No. 7 are withdrawn.

11. No claims allowed.

12 **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
June 13, 2003